

## REMARKS

Entry of the above-made amendments and reconsideration of the present application are respectfully requested. Upon entry of the amendments, this application will contain claims 1-35. Of these, claims 1-20, 30, 32 and 33 are under consideration. Claims 21-29, 31, 34, and 35 stand withdrawn, but are method claims that are subject to potential rejoinder. For the reasons discussed herein, it is submitted that the rejections of record are overcome, and that this application is in condition for allowance. Action to that end is therefore solicited.

### Restriction/Election (paragraphs 1-2)

With regard to paragraphs 1-2, the finality of the election requirement is noted by Applicants. Applicants elect not to pursue any petition of the election requirement, and acknowledge with appreciation the Examiner's rejoinder of Groups II and III to Group I.

### Trademarks (paragraphs 3-4)

With regard to the trademark SPECTRAMAX, the specification has been amended to use the all-caps version of the mark. The specification has been reviewed and other trademark uses that were noted have been similarly amended.

#### Information Disclosure Statement (paragraph 5)

The Examiner's remarks regarding listings of references in the specification are noted. Applicants intend to submit an IDS in the near future including copies of the listed references.

#### Rejections Under 35 USC 112, second paragraph (paragraph 7)

Claims 1-15, 30, 32 and 33 stand rejected under 35 USC 112, second paragraph, for indefiniteness. To the extent maintained, these rejections are respectfully traversed for the following reasons.

In regard to claim 30, it is asserted in the Office Action that this claim is indefinite for reciting "wherein the liquid carrier is a pharmaceutically acceptable liquid carrier", based on the assertion that there is no prior recitation of a liquid carrier (antecedent basis). In response, the Examiner is requested to consider that claim 30 depends from claim 1, and thus incorporates all of the limitations of claim 1. Claim 1, in turn, does recite a "liquid carrier". It is therefore believed that proper antecedent basis is present, and that claim 30 is not objectionable under 35 USC 112, second paragraph.

In regard to claim 33, the Office Action asserts that this claim is indefinite for reciting "A pharmaceutical composition according to claim 32, which is an ultrasound contrast agent". While it is believed that the prior language of the claim was clear (overall microbubble compositions are commonly referred to in the art as contrast agent compositions), claim 33 has been amended to specify that the microbubbles are effective to provide an ultrasound contrast agent.

In regard to claim 1 (and thus its dependent claims 2-8), the Office Action asserts that the use of a phrase including "crenated microbubble membranes" renders the claim indefinite. It is believed that those of ordinary skill in the art would understand this terminology of the claims. However, to advance the present prosecution, claim 1 has been amended to recite "microbubble membranes having exterior surfaces comprising outwardly-projecting wrinkles formed of excess membrane material". This terminology is supported throughout the application, and introduces no new subject matter. Likewise, the remainder of the amendments to claim 1 and other claims are supported throughout the application, including in other original claims, and introduce no new subject matter.

In regard to claim 9 (and thus its dependent claims 10-15), the Office Action asserts that the use of "microbubble membranes having surface projections" renders the claim indefinite. It is believed that those of ordinary skill in the art would understand this terminology. However, to advance the present prosecution, claim 9 has also been amended to recite "microbubble membranes having exterior surfaces comprising outwardly-projecting wrinkles formed of excess membrane material".

In view of the foregoing, withdrawal of the rejections under 35 USC 112, second paragraph, is solicited.

#### Rejections Under 35 USC 102 (paragraphs 8-11)

Claims 16-20 stand rejected under 35 USC 102 (b or e) over U.S. Patent No. 6,193,951 (the '951 patent). This rejection is respectfully traversed.

To anticipate a claim, a reference must disclose every limitation of that claim. Claims 16-20, as amended, include the feature of: "said microbubbles having non-spherical microbubble membranes having exterior surfaces comprising outwardly-projecting wrinkles formed of excess membrane material". The '951 patent does not teach this claimed feature. The '951 patent thus does not anticipate claims 16-20, and withdrawal of this rejection is solicited.

#### Rejections Under 35 USC 103 (paragraphs 12-13)

Claims 1-20, 30, 32 and 33 stand rejected under 35 USC 103 over U.S. Patent No. 6,372,195 (the '195 patent) in view of U.S. Patent No. 6,548,048 (the '048 patent). To the extent maintained against the claims as amended, this rejection is respectfully traversed for the following reasons.

The rejected claims require a combination of features that is not disclosed or suggested by the '195 and '048 patents, considered alone or together. These claims require:

1. That at least 20% of the microbubbles in the liquid carrier are nonspherical microbubbles having microbubble membranes with exterior surfaces comprising outwardly-projecting wrinkles formed of excess membrane material;

2. That the nonspherical microbubbles exhibit increased deformability under shear relative to corresponding spherical microbubbles; and
3. That the membranes include targeting molecules that bind to the target.

As disclosed in the present application, and demonstrated in its actual working Experimental, the combination of the wrinkles, increased deformability, and the targeting molecules, substantially increases the efficacy of targeting of the microbubbles as compared to corresponding spherical microbubbles. In this regard, reference can be made, for example, to Figure 8 and Figures 9A-C which show comparative *in vitro* firm attachment events and pause time, respectively, for wrinkled and spherical microbubbles. The corresponding experimental and result descriptions are found in sections 1.8.1 and 1.8.2 (experimental) and 2.3.2 and 2.3.3 (results) of the Experimental. As described, the inventive microbubbles show significantly higher rates of firm attachments and greater pause times, evidencing an improved targeting function. Further, comparative *in vivo* target adherence results for wrinkled and spherical microbubbles are shown in Figure 11, and again demonstrate that substantially improved targeting can be achieved by the present claimed microbubbles. The corresponding experimental and result descriptions are found in sections 1.9 and 2.5 of the Experimental, respectively. The prior art is devoid of any such teaching.

Specifically, neither the '195 patent nor the '048 patent teaches or suggests the feature that the nonspherical microbubbles exhibit increased deformability under shear relative to corresponding spherical microbubbles, much less the unexpected finding that such deformability can be used in enhancing targeting when targeting molecules are incorporated in the bubble membranes.

Further, with regard to the claimed feature of "nonspherical microbubbles having microbubble membranes with exterior surfaces comprising outwardly-projecting wrinkles formed of excess membrane materials", neither the '195 patent nor the '048 patent teaches or suggests targeting microbubbles having such features and that when they do, enhanced targeting results. Again, these teachings can only be found in the present application.

With regard to the teachings of the '195 patent, the remarks in the Office Action assert that based on the statement that the volume of the microbubbles in the '195 patent is reduced, they appear to be "the same or similar" to the microbubbles set forth in the prior claim language. It is submitted that this extension of the '195 patent appears somewhat tenuous, even more so if considered against the claims as amended. The pertinent patent law jurisprudence requires that for a feature to be found inherent in the prior art, it must *necessarily* occur – possibilities or probabilities are not enough. Further, the Examiner is asked to take note that those of ordinary skill in the art at the time the present invention was made would more likely have expected that upon loss of gas volume, the microbubbles would rapidly transition and shed excess

membrane material to again take on a spherical shape. Thus, the ordinarily skilled artisan would never have been equipped with information necessary to realize that the claimed wrinkled microbubbles should be prepared and should incorporate a targeting molecule to improve adherence to the target.

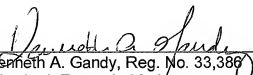
In this regard, the thermodynamics involved in the assembly of gas-filled microbubble structures stabilized by amphipathic surfactants (such as phospholipids) prescribe that the structures adopt a formation which minimizes free energy, i.e. a sphere. Consistently, literature in the area has taught that loss of gas through the shell of a lipid-encapsulated microbubble results in commensurate shedding of shell components and reversion to a spherical form. For example, shrinking microbubbles were observed to remain spherical during gas loss through the shell by Borden and colleagues (Borden et al, *Langmuir* 2002, 18, 9225), and shedding of lipid vesicles during gas loss was observed by Pu (Pu et al, *Langmuir* 2006, 22, 2993-2999) and Gopal (Gopal et al, *J. Phys Chem B* 2001, 105: 10348). Copies of these articles are attached for the Examiner's consideration. Thus, it is reasonable that one ordinarily skilled in the art considering the '195 patent would not necessarily expect that loss of gas volume from a microbubble would result in a stable wrinkled microbubble as in the present application, but rather a smaller, though still spherical, microbubble. Accordingly, those of ordinary skill in the art reading the '195 patent would not be equipped with information that would motivate them to make the present claimed targeted microbubbles or to expect their improved targeting properties. Those teachings can only be derived from the present application.

For the above reasons, the Examiner is requested to reconsider and withdraw the rejections made under 35 USC 103.

Conclusion

For the foregoing reasons, it is believed that all rejections made in the Office Action have been addressed and overcome. Reconsideration and allowance of the application, as amended, are earnestly solicited. The Examiner is invited to contact the undersigned attorney by telephone if there are any questions concerning this submission or any other matters that may be handled in that fashion to expedite the allowance of this application.

Respectfully submitted,

By   
Kenneth A. Gandy, Reg. No. 33,386  
Woodard, Emhardt, Moriarty,  
McNett & Henry LLP  
111 Monument Circle, Suite 3700  
Indianapolis, Indiana 46204-5137  
(317) 634-3456